Complete Summary

GUIDELINE TITLE

Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions.

BIBLIOGRAPHIC SOURCE(S)

Casey C, Vellozzi C, Mootrey GT, Chapman LE, McCauley M, Roper MH, Damon I, Swerdlow DL. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Recomm Rep 2006 Feb 3;55(RR-1):1-16. [43 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Adverse events after smallpox vaccination, including

- Superinfection of the vaccination site or regional lymph nodes
- Inadvertent autoinoculation (nonocular)
- Contact transmission (nonocular)
- Ocular vaccinia
- Eczema vaccinatum
- Progressive vaccinia
- Erythema multiforme major or Stevens-Johnson Syndrome
- Fetal vaccinia
- Postvaccinial central nervous system disease
- Myo/pericarditis

- Dilated cardiomyopathy

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management

CLINICAL SPECIALTY

Allergy and Immunology
Dermatology
Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Ophthalmology
Pathology
Pediatrics
Pharmacology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Health Care Providers
Nurses
Patients
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To provide uniform criteria used for the surveillance case definition and classification for adverse events and reactions associated with smallpox vaccination

TARGET POPULATION

Persons presenting with adverse reactions or adverse events after smallpox vaccination

INTERVENTIONS AND PRACTICES CONSIDERED

1. Use of surveillance case definitions and classification system utilizing, as appropriate
    - History and physical examination
    - Laboratory results
    - Radiographic findings

2. Reporting of adverse events associated with smallpox vaccination to the Vaccine Adverse Events Reporting System (VAERS)

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The joint Advisory Committee on Immunization Practices (ACIP)-Armed Forces Epidemiological Board (AFEB) Smallpox Vaccine Safety Working Group (SVS WG) was responsible for safety oversight of the Department of Health and Human

Services (DHHS) and Department of Defense (DoD) smallpox preparedness programs. The majority of the case definitions for vaccinia adverse reactions were drafted by the Vaccinia Case Definition Development working group in collaboration with ACIP-AFEB SVS WG. The Vaccinia Case Definition Development working group membership included Centers for Disease Control and Prevention (CDC) and DoD medical epidemiologists, smallpox eradication experts, ophthalmologists, dermatologists, cardiologists, and infectious-disease specialists. These work groups contributed to the development of case definitions by completing literature searches, translating publications, coordinating or participating in meetings, collecting or analyzing data, investigating cases, providing subject-matter expertise, and drafting and revising case definitions. The case definition for fetal vaccinia was developed by CDC and DoD for use in the development of the National Smallpox Vaccine in Pregnancy Registry.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Not stated

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not applicable

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Introduction

Surveillance guidelines that include standardized case definitions for reporting of notifiable infectious diseases are important public health tools that contribute to the assessment of disease trends, measurement of intervention effectiveness, and detection of disease outbreaks. Comparable surveillance guidelines for the classification and reporting of adverse reactions after vaccination are nominal and have not commonly included standardized case definitions. The term vaccine-related "complication" is often used interchangeably with the terms "side effects" or "adverse reaction" and should be distinguished from the term "adverse event." An adverse reaction is an untoward effect that occurs after a vaccination and is extraneous to the vaccine's primary purpose of producing immunity (e.g., eczema vaccinatum). Adverse reactions have been demonstrated to be caused by the vaccination. In contrast, adverse events are untoward effects observed or reported after vaccinations, but a causal relation between the two have yet to be established. This report focuses on adverse reactions known to be caused by

smallpox vaccine (with the exception of dilated cardiomyopathy that has not been shown to have a causal relation) on the basis of scientific evidence. Uniform criteria for classification of adverse reaction reports after smallpox (vaccinia) vaccination have been established. Criteria for dilated cardiomyopathy, an adverse event (not shown to have a causal relation with smallpox vaccination), also have been established. These case definitions and reporting guidelines were used by the Centers for Disease Control and Prevention (CDC) and the Office of the Assistant Secretary of Defense for Health Affairs during the mandatory Department of Defense (DoD) and voluntary U.S. Department of Health and Human Services (DHHS) smallpox vaccination programs that were designed to increase national preparedness in the event of a biologic terrorism attack.

This report describes the case definitions used to classify reported adverse events during the DHHS smallpox vaccination program. The overall safety surveillance system and related findings are reported elsewhere.

Reporting Guidelines

The following surveillance case definitions establish reporting criteria for prospective or retrospective classification of cases. Clinical, laboratory, and epidemiologic information are necessary for accurate case classification, which could not be obtained without cooperation and information exchange between treating health-care providers, state health officials, laboratorians, and the CDC. Any adverse event after smallpox vaccination should be reported to state health departments and the Vaccine Adverse Events Reporting System (VAERS), particularly those events known to be adverse reactions (see Table below). Any adverse reaction that requires treatment with vaccine immune globulin (VIG) or cidofovir should be reported immediately, and adverse events that meet the regulatory criteria for "serious" (i.e., those resulting in hospitalization, permanent disability, life-threatening illness, or death) should be reported within 48 hours; all other events should be reported within 1 week. Reports can be submitted to VAERS at http://www.vaers.hhs.gov, 877-721-0366, or P.O. Box 1100, Rockville, MD 20849-1100. Report forms and assistance with reporting are available from VAERS (800-822-7967).

Table. Adverse Events After Smallpox Vaccination That Are Recommended to be Reported to the Vaccine Adverse Event Reporting System and to State Health Departments[1]

- Superinfection of the vaccination site or regional lymph nodes[2]
- Inadvertent autoinoculation (nonocular)
- Contact transmission (nonocular)
- Ocular vaccinia
- Generalized vaccinia
- Eczema vaccinatum
- Progressive vaccinia
- Erythema multiforme major or Stevens-Johnson Syndrome[3]
- Fetal vaccinia
- Postvaccinial central nervous system disease
- Myo/pericarditis
- Dilated cardiomyopathy[4]

[1] Any adverse event that is of concern to the clinician or patient should be reported.
[2] Previously referred to as pyogenic infection of vaccination site
[3] Clinically defined
[4] Causal association with smallpox vaccination has not been shown.

Case Definition and Classification

For all cases, exposure to vaccinia is required; vaccination, close contact with a recent vaccinee, or intrauterine exposure can fulfill this criterion. Vaccinia virus can be transmitted from the vaccination site to close contacts of persons who received smallpox vaccine, and these contacts can experience the same adverse reactions as vaccinees.

Smallpox vaccine adverse events can be divided into several categories. Localized reactions include a superinfection of the vaccination site or regional lymph nodes and robust take (RT). Unintentional transfer of vaccinia virus includes transfer from the vaccination site to elsewhere on the vaccinee's body and is called inadvertent autoinoculation. When the virus is transferred from the vaccinee to a close contact, it is called contact transmission. In either case, if the virus is transferred to the eye and surrounding orbit, it is referred to as ocular vaccinia. Diffuse dermatologic complications include two groups. The first group (hypersensitivity rashes) includes nonspecific, postvaccination rash, erythema multiforme minor, and Stevens-Johnson syndrome. These lesions are not thought to contain vaccinia virus, and because these terms are defined elsewhere in the dermatologic literature, they are not included in this report. The second group of diffuse dermatologic complications is thought to be caused by replicating vaccinia virus that can be recovered from the rash of generalized vaccinia (GV) (usually a benign, self-limiting condition), eczema vaccinatum (EV) (often associated with substantial morbidity), and progressive vaccinia (PV) (which is generally fatal). Rare adverse reactions include fetal vaccinia and postvaccinial central nervous system diseases such as post-vaccinial encephalitis or encephalomyelitis. Other reactions previously reported but not well described include the newly characterized cardiac adverse reaction, myo/pericarditis (M/P) or the newly described cardiac adverse event dilated cardiomyopathy (DCM), which has not been yet been demonstrated to be etiologically linked.

Localized Reactions

Superinfection of the Vaccination Site or Regional Lymph Nodes

Surveillance Case Definition for Superinfection of the Vaccination Site or Regional Lymph Nodes After Smallpox Vaccination for Use in Smallpox Vaccine Adverse Event Monitoring And Response

Superinfection of the vaccination site or regional lymph nodes is defined as a nonvaccinial superinfection (e.g., superinfection caused by bacterial, fungal, atypical, or viral organisms) that produces a local inflammatory response at the site of vaccination and can present with the same signs and symptoms as vaccinia virus replication at the vaccination site. Case definition for superinfection of the vaccination site or regional lymph nodes

A suspected case of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:

- Vaccination site or regional lymph nodes with three or more of the following findings:
  - Dolor (pain and/or tenderness)
  - Calor (warmth)
  - Rubor (redness)
  - Other (regional lymphadenopathy; lymphangitic streaking; edema, induration, and/or swelling; fluctuance; and blister with pus or honey-crusted plaque)

  and

- Temporal criterion:
  - Onset or peak symptoms occur from day of vaccination to day 5 after vaccination and/or day 13-60 after vaccination (excludes days 6-12 after vaccination)

  and

- Clinical course:
  - Clinical criteria persist or worsen for hours to days after vaccination; patient report is adequate.

A confirmed case of superinfection of the vaccination site or regional lymph nodes is defined by the following criteria:

- Vaccination site or regional lymph nodes with three or more of the following findings:
  - Dolor (pain and/or tenderness)
  - Calor (warmth)
  - Rubor (redness)
  - Other (regional lymphadenopathy; lymphangitic streaking; edema, induration, and/or swelling; fluctuance; and blister with pus or honey-crusted plaque)

  and

- Temporal criterion:
  - Symptoms occur from day of vaccination to 60 days after vaccination (inclusive)

  and

- Laboratory criteria having one or more of the following findings:
  - Positive results of pathogenic culture (e.g., bacterial, fungal, atypical, or nonvaccinial viral culture)
  - Positive microscopy results (e.g., Gram stain, silver stain, acid-fast bacillus stain, or darkfield)

- Positive result of bioburden testing[1] of the vaccinia vaccine vial

or

- Radiographic findings:
  - Findings consistent with superinfection (e.g., lymphadenopathy or abscess) by magnetic resonance imaging, computed tomography scan, or ultrasound.

[1] Bioburden is referred to as the number of microorganisms on a contaminated object; it is also called bioload. For testing of vaccinia vaccine vial, a positive bioburden test indicates that the accepted limits of bioload have been exceeded and the vaccine is not suitable for use.

Unintentional Transfer of Vaccinia Virus

Inadvertent Autoinoculation

Surveillance Case Definition for Inadvertent Autoinoculation (Nonocular) for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Inadvertent autoinoculation occurs when a person who has received smallpox vaccine or experienced inoculation from contact might physically transfer vaccinia virus from vaccination or contact site to another part of the body through scratching or through inanimate objects such as clothing, dressings, or bedding. The most common sites of inadvertent autoinoculation, nonocular are the face, nose, mouth, lips, genitalia, and anus. Lesions at autoinoculation sites progress through the same papular, vesicular, and pustular stages as the vaccination site. When autoinoculation occurs more than 5 days postvaccination, the developing immune response might attenuate the lesions and their progression. Persons at highest risk for inadvertent autoinoculation are children aged 1-4 years and those with disruption of the epidermis, including, but not limited to, abrasions or burns.

Case definition for inadvertent autoinoculation (nonocular)

A suspected case of inadvertent autoinoculation is defined by the following criteria:

- Affected person has been recently vaccinated and had one or more lesions at one or more sites beyond the boundaries of the dressing that was used. Lesions progress morphologically through papule, vesicle, pustule, and scab,* and
- Lesions appear up to 10 days after the period beginning with initial vaccination or contact through final resolution and scarring of lesions at vaccination or contact inoculation site.

A probable case of inadvertent autoinoculation meets the criteria for a suspected case and

- Does not meet the case definition for generalized vaccinia*, eczema vaccinatum, or progressive vaccinia, and

- Other likely etiologies (e.g., bacterial or viral infection) have been excluded.

A confirmed case of inadvertent autoinoculation meets the criteria for a suspected or probable case of inadvertent autoinoculation and has the following laboratory evidence of vaccinia infection (on the basis of testing skin lesions distant from the vaccination site in a vaccinee):

- Positive test results for vaccinia polymerase chain reaction (PCR) assay or antigen detection techniques (e.g., direct fluorescent assay or direct fluorescent antibody)

  or

- Demonstration of vaccinia virus by culture

Note: Histopathologic examination showing typical orthopox cytopathic changes or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent PCR or culture.

*Generalized vaccinia should be considered if ≥20 lesions are present.

Contact Transmission

Surveillance Case Definition for Contact Transmission (Nonocular) for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Contact transmission of vaccinia virus occurs when virus shed from smallpox vaccination sites or from distant lesions in persons with inadvertent autoinoculation, generalized vaccinia (GV), eczema vaccinatum (EV), or progressive vaccinia (PV) is transferred to another person. Virus might be shed until the scab heals. The virus can survive for several days on clothing, bedding, or other inanimate surfaces. An unvaccinated or nonrecently vaccinated person in close contact (i.e., touching a person's lesions or vaccination site, clothing, bedding, or bandages) with a vaccinee or their inanimate objects might acquire vaccinia infection. Infection acquired through contact transmission can result in inadvertent autoinoculation from the exposure site to additional sites (including ocular vaccinia) or can result in other adverse reactions.

Case definition for contact transmission (nonocular)

A suspected case of contract transmission is defined as

- The development of one or more lesions that progress through papule, vesicle, or pustule stages
- History of close contact with
  - Someone who has received the vaccine <3 weeks before the exposure, or
  - Someone who has had autoinoculation GV, EV, and PV diagnosed; and
  - Lesions appear 3-9 days after vaccinia exposure.

A probable case of contact transmission meets the case definition for suspected case, and other likely etiologies (e.g., bacterial or viral infection) have been excluded.

For a confirmed case of contact transmission, laboratory evidence of vaccinia infection exists on the basis of testing skin lesions in a close contact of a known vaccinee. Laboratory evidence of vaccinia infection includes

- Positive test results for vaccinia polymerase chain reaction (PCR) assay or antigen detection techniques (e.g., direct fluorescent antibody)

  or

- Demonstration of vaccinia virus by culture

Note: Histopathologic examination showing typical orthopox cytopathic changes or electron microscopy of biopsy specimens revealing orthopox virus is strongly suggestive of infection with vaccinia and should be confirmed by subsequent PCR or culture.

Ocular Vaccinia

Surveillance Case Definition for Ocular Vaccinia for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Ocular vaccinia is the appearance of lesions suspicious for vaccinia in or near the eye in a vaccinee (or close contact of a vaccinee) up to 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site, to include periocular[1] involvement, lid involvement (blepharitis[2]), conjunctival involvement (conjunctivitis[3]), and/or corneal involvement (keratitis[4]).

Case definition for ocular vaccinia

A suspected case of ocular vaccinia is defined as the new onset of erythema or edema of the conjunctiva (conjunctivitis), eyelid (blepharitis), or periocular area or inflammation of the cornea (keratitis) in a recent vaccinee (or close contact of vaccinee) that cannot be ascribed to another ocular diagnosis

and

- Temporal criteria of
  - Onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site

    or

  - Onset during the presence of visible vaccinia lesions before scab separation

A probable case of ocular vaccinia is the presentation in or near the eye of lesions consistent with vaccinia infection to include formation of vesicles that progress to pustules that umbilicate and indurate in a manner similar to a normal vaccinia reaction (Note: see exceptions/differences to conjunctival and cornea clinical presentation footnotes 3 and 4)

and

- Temporal criteria of
  - Onset after vaccinia exposure but not more than 10 days after the period beginning with initial vaccinia exposure through final resolution and scarring of lesions at vaccination site or exposure site

    or

  - Onset during the presence of visible vaccinia lesions before scab separation

A confirmed case of ocular vaccinia meets the criteria as a probable or suspected case of ocular vaccinia with laboratory evidence of vaccinia infection (testing lesions on or near the eye). Laboratory evidence includes

- Positive test results for vaccinia polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody)

  or

- Demonstration of vaccinia virus by culture

[1] Periocular involvement (generally above the brow or below the inferior orbital rim) Papules, vesicles, or pustules not involving the ocular adnexa, lids, lid margins, or canthi.
[2] Blepharitis: (lid involvement): Mild--few pustules, mild edema, and no fever; Severe--pustules, edema, hyperemia, lymphadenopathy (preauricular or submandibular), cellulitis, and fever.
[3] Conjunctivitis (involvement of membrane that lines inner surface of the eyelid and exposed surface of the eyeball, excluding the cornea): Conjunctiva might be inflamed (red) with serous or mucopurulent discharge if lesions involve the conjunctiva or cornea. Symptoms of ocular irritation (foreign body sensation) might be present with onset of erythema. Conjunctival lesions typically form vesicles that rapidly ulcerate and form raised "moist appearing" white lesions (rather than pustules that scab) before final resolution: Mild--mild hyperemia or edema, no membranes or focal lesions; Severe--marked hyperemia, edema, membranes, focal lesions, lymphadenopathy (preauricular and/or submandibular), and fever.
[4] Keratitis (corneal involvement): Corneal lesions might present as a grey-appearing superficial punctuate keratitis that might later coalesce to form a geographic epithelial defect resembling herpes simplex keratitis. Stromal corneal lesions might present as small subepithelial opacities resembling those observed in epidemic keratoconjunctivitis, might be associated with epithelial defect, and might progress to corneal haze/clouding: Mild--grey epitheliitis, no epithelial defect, and no stromal haze or infiltrate (cloudy cornea); Moderate--epithelial defect; Severe--ulcer, stromal haze, or infiltrate.

Generalized Vaccinia

Surveillance Case Definition for Generalized Vaccinia After Smallpox Vaccination for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Generalized vaccinia (GV) is a disseminated vesicular or pustular rash appearing anywhere on the body ≥4 days after smallpox vaccination and might be accompanied by fever. GV also can appear as a regional form that is characterized by extensive vesiculation around the vaccination site or as an eruption localized to a single body region. The skin lesions of GV are thought to contain virus spread by the hematogenous route. Primary vaccinees are at higher risk for GV than revaccinees. GV is usually self-limited among immunocompetent hosts. Vaccinia immune globulin (VIG) might be beneficial in the rare case where an immunocompetent person appears systemically ill. GV is often more severe among persons with underlying immunodeficiency, and these patients might benefit from early intervention with VIG.

Notes:

1. Systemic symptoms might be present.
2. At early onset of some cases, skin lesions might be macules or slightly elevated papules; in late cases, lesions might have developed scabs.
3. History or clinical signs of eczema/atopic dermatitis or Darier's disease or severe illness should prompt evaluation for eczema vaccinatum.
4. Presence of acute or chronic exfoliative, erosive, or blistering skin disease (e.g., acute burn and epidermolytic hyperkeratosis) should prompt consideration of multiple inadvertent inoculations.
5. A vaccinial skin eruption characterized by grouped vesicles or pustules close to or surrounding the vaccination site but do not appear to be satellite lesions (e.g., on the basis of the presence of a large number of lesions and evidence that the lesions are caused by hematogenous spread of vaccinia) might constitute a regional form of generalized vaccinia.

Case definition for generalized vaccinia

A probable case of generalized vaccinia occurs in persons recently vaccinated or in a close contact of a recent vaccinee and meets the following criteria:

- A vesicular or pustular eruption at one or more body areas distant from the vaccination site or inadvertent inoculation site
- Skin eruption occurring approximately 4-19 days after smallpox vaccination or contact with someone vaccinated against smallpox
- Lesions follow approximately the same morphologic progression as a primary vaccination site (i.e., papule, vesicle, pustule, scab, and scar)
- Unlikely that autoinoculation accounts for skin eruption
- Other likely etiologies have been excluded.

A confirmed case of generalized vaccinia can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and no laboratory evidence of vaccinia infection (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site [if identifiable]) exists in a close contact of a known vaccinee or in a patient who is not known to be a close contact.

- Laboratory evidence of vaccinia infection includes
    - Demonstration of vaccinia virus by culture

or

- Histopathologic examination shows typical orthopox cytopathic changes, and either polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

Eczema Vaccinatum

Surveillance Case Definition for Eczema Vaccinatum After Smallpox Vaccination for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Eczema vaccinatum (EV) is a localized or generalized papular, vesicular, pustular, or erosive rash syndrome that can occur anywhere on the body, with a predilection for areas currently or previously affected by atopic dermatitis lesions. Persons with a history of atopic dermatitis are at highest risk for EV. Onset of the characteristic lesions can be noted either concurrently with or shortly after the development of the local vaccinial lesion in vaccinees. EV cases resulting from secondary transmission usually appear with skin eruptions approximately 5-19 days after the suspected exposure. EV lesions follow the same dermatologic course (progression) as the vaccination site in a vaccinee, and confluent or erosive lesions can occur. The rash is often accompanied by fever and lymphadenopathy, and affected persons are frequently systemically ill. EV tends to be most severe among first-time vaccinees, young children, and unvaccinated close contacts of vaccinees. Before the availability of vaccinia immune globulin (VIG), this condition had a high mortality. Establishing the diagnosis early and treating with VIG is crucial in reducing mortality.

Notes:

1. Although a history consistent with eczema/atopic dermatitis or Darier's disease (i.e., keratosis follicularis) is included in the surveillance definition for EV, clinicians evaluating vaccinees or close contacts of recent vaccinees with a presentation consistent with EV who do not report having one of these dermatologic conditions should still consider EV as a clinical diagnosis and assess for treatment with VIG.
2. Lesions of EV are in approximately the same stage of morphologic development as each other and progress.

Case definition for eczema vaccinatum

A probable case of EV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- A history of or current exfoliative skin condition consistent with a diagnosis of eczema/atopic dermatitis or Darier's disease

  and

- Multiple skin lesions that developed
    - In a vaccinated person concurrently or soon after lesion at vaccination site or in a close contact of a recent vaccinee up to 3 weeks after exposure, if time of relevant exposure is known
    - Are distant from the vaccination or likely inoculation site (i.e., are unlikely to be satellite lesions)

      and

    - Are or have become vesicular/pustular sometime during their evolution (i.e., do not remain macular or papular). Erosive or ulcerative lesions might be observed.

  and

- Other likely etiologies have been excluded such as eczema herpeticum (which can be particularly difficult to distinguish), smallpox, chickenpox, disseminated herpes zoster, or pustular (bacterial) impetigo.

A confirmed case of EV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a probable case and laboratory evidence of vaccinia infection exists (on the basis of testing skin lesions distal from vaccination site in a vaccinee or distal to likely inoculation site, if identifiable) in a close contact of a known vaccinee or in a patient who is not known to be a close contact.

- Laboratory evidence of vaccinia infection includes
    - Demonstration of vaccinia virus by culture

      or

    - Polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia, histopathologic examination showing typical orthopox cytopathic changes, and electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

Progressive Vaccinia

Surveillance Case Definition for Progressive Vaccinia for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Progressive vaccinia (PV) refers to continued vaccinia virus replication with progressive infection of skin surrounding the vaccination site or inadvertent inoculation site and sometimes the occurrence of secondary metastatic lesions in a person with underlying immune deficit (humoral or cellular). The condition is rare, severe, and often lethal. The description of the vaccination site lesion is usually that of a necrotic lesion; however, this is not the only presentation described with PV.

Lesions can appear "clean," fungated, piled-up, well-demarcated, or have bacterial superinfection.

Case definition for progressive vaccinia

A suspected case of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- Have a known or suspected depressed or defective immune system (suspicion might arise as result of clinical suspicion of PV)

  and

- Have a vaccination site lesion or inadvertent inoculation site with one of the following criteria:
  - No or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion
  - Progressive expansion at or after 15 days of vaccination, or
  - Failure to heal or failure of lesion to regress at or after 15 days of vaccination

  and

- Other likely etiologies (e.g., bacterial superinfection) have been excluded.

A probable case of PV occurs in persons recently vaccinated or in a known close contact of a recent vaccinee and meets the following criteria:

- A known or suspected depressed or defective immune system

  and

- A vaccination site lesion or inadvertent inoculation site with one of the following criteria:
  - No or minimal inflammatory response around lesion associated with a nonhealing or enlarging vaccination lesion
  - Progressive expansion at or after 21 days of vaccination, or
  - Failure to heal or failure of lesion to regress at or after 21 days of vaccination

  and

- Other likely etiologies (e.g., bacterial superinfection) have been excluded.

A confirmed case of PV can occur in a recent vaccinee, a known close contact of a recent vaccinee, or someone with no known contact but who otherwise meets the criteria for a suspected case and laboratory evidence of vaccinia infection (on the basis of testing skin lesions at least 15 days after vaccination or likely time of inoculation in a close contact of a recent vaccinee or in persons with no known contact with a vaccinee) exist

Laboratory evidence of vaccinia infection include

- Demonstration of vaccinia virus by culture

  or

- Histopathologic examination showing typical orthopox cytopathic changes, and either polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody) revealing vaccinia or electron microscopy of biopsy specimens revealing orthopox virus are strongly suggestive of infection with vaccinia and should be confirmed by subsequent culture.

Rare Reactions

Fetal Vaccinia

Surveillance Case Definition for Fetal Vaccinia for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Fetal vaccinia is a rare but serious complication resulting from vaccinia infection in utero that can occur in any trimester of pregnancy. It has been characterized by the presence of multiple skin lesions, including macules, papules, vesicles, pustules, scars, ulcers, areas of maceration, and epidermolysis (blisters or bullae). When fetal vaccinia occurs, the outcome is usually fetal death, stillbirth, or premature birth of a neonate that dies shortly after birth. Survival of babies with apparent in utero infection such as scarring has also been described. Vaccinia infection in products of conception occurs rarely.

Case definition for fetal vaccinia

A suspected case of fetal vaccinia is the presence of any skin lesion in a fetus or newborn exposed to vaccinia virus in utero and no other attributable cause.

A probable case of fetal vaccinia is the presence of multiple skin lesions that might include macules, papules, vesicles, pustules, scars, ulcers, areas of maceration, or epidermolysis (blisters/bullae) in a fetus or newborn exposed to vaccinia in utero and no other attributable cause.

A confirmed case of fetal vaccinia meets the criteria for a probable case and has laboratory evidence for vaccinial infection:

Laboratory criteria for diagnosis includes

- Positive test results for vaccinia virus by polymerase chain reaction assay or antigen detection techniques (e.g., direct fluorescent antibody), or
- Demonstration of vaccinia virus by culture

Vaccinia infection: Fetus, newborn, or product of conception with laboratory evidence of infection and without any clinical symptoms or signs.

Postvaccinial Central Nervous System Disease

Surveillance Case Definition for Postvaccinial Central Nervous System Disease After Smallpox Vaccination for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Postvaccinial central nervous system disease is an inflammation of the parenchyma of the central nervous system after smallpox vaccination. When the inflammation occurs in the brain it is called "encephalitis," and when it occurs in the spinal cord it is called "myelitis." Confirmation of diagnosis is made only on the basis of the demonstration of central nervous system (CNS) inflammation by histopathology or neuroimaging, but might be suggested by clinical features.[1]

Case definition for encephalitis

A suspected case of encephalitis is defined as the presence of the acute onset of

- Encephalopathy (e.g., depressed or altered level of consciousness, lethargy, or personality change lasting >24 hours)
- Clinical evidence suggestive of cerebral inflammation to include one of the following:
    - Fever (temperature >100°F [>38°C]) or hypothermia (temperature <95°F [<35°C])
    - Meningismus (i.e., nuchal rigidity and photo/phonophobia)
    - Cerebrospinal fluid (CSF) pleocytosis (>5 white blood cells/mm^3)
    - Presence of focal neurologic deficit
    - Electroencephalography findings consistent with encephalitis
    - Neuroimaging findings on magnetic resonance imaging consistent with acute inflammation (with or without meninges) or demyelination of the nervous system
    - Seizures (either new onset or exacerbation of previously controlled seizures)

and

- No alternative (investigated) etiologies are found for presenting sign and symptoms.

A probable case of encephalitis is defined by the acute onset of

- Encephalopathy as outlined for a suspected case

and

- Two or more of the criterion listed for suspected encephalitis as clinical evidence suggestive of cerebral inflammation

and

- No alternative (investigated) etiologies are found for presenting sign and

symptoms

A confirmed case of encephalitis is defined as

- Demonstration of acute cerebral inflammation (with or without meninges) or demyelination by histopathology

  and

- No alternative (investigated) etiologies are found for presenting sign and symptoms

Case definition for acute myelitis

A suspected case of myelitis is defined as presence of the acute onset of

- Myelopathy (development of sensory, motor, or autonomic dysfunction attributable to the spinal cord, including upper- and lower-motor neuron weakness, sensory level, and bowel or bladder dysfunction)

  and

- Additional evidence suggestive of spinal cord inflammation, to include one of the following:
  - Fever (temperature >100ºF [>38ºC]) or hypothermia (temperature <95°F [<35°C])
  - CSF pleocytosis (>5 white blood cells/mm^3)
  - Presence of focal neurologic deficit
  - Electromyographic (EMG) studies suggestive of central (spinal cord) dysfunction
  - Neuroimaging findings on MRI demonstrating acute inflammation (with or without meninges) or demyelination of the spinal cord

  and

- No alternative (investigated) etiologies are found for presenting sign and symptoms.

A probable case of myelitis is defined by the acute onset of

- Myelopathy as outlined for a suspected case

  and

- Two or more of the criterion listed for suspected myelitis as evidence suggestive of spinal cord inflammation

  and

- No alternative (investigated) etiologies are found for presenting sign and

symptoms.

A confirmed case of myelitis is defined by

- Demonstration of acute spinal cord inflammation (with or without meninges) or demyelination by histopathology

  and

- No alternative (investigated) etiologies are found for presenting sign and symptoms.

Note: Cases fulfilling the criteria for both encephalitis and myelitis in any category would be classified as encephalomyelitis.

[1] Some cases of postvaccinial encephalomyelitis might be caused by direct infection of the CNS by vaccinia virus, resulting in acute cytotoxic neuronal damage and inflammation. However, laboratory evidence of virus replication is lacking in the majority of cases and might be attributable to immunopathological mechanisms instead. In the majority of cases, histopathologic findings similar to other "postinfectious" encephalitides are found, suggestive of an inflammatory demyelinating condition (acute disseminated encephalitis/encephalomyelitis [ADEM]). The distinction between these two pathologic mechanisms might be difficult to make clinically in the early stages of illness. A diagnosis of ADEM might be favored by a longer interval of onset after vaccination; magnetic resonance imaging findings of multifocal areas of increased signal on T2, fluid attenuation inversion recovery, and diffusion weighted imaging sequences, suggestive of acute demyelination; and an absence of CSF pleocytosis.

Cardiac

Myo/pericarditis

Surveillance Case Definition for Myo/pericarditis for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Myo/pericarditis

Myo/pericarditis is defined as a spectrum of disease caused by inflammation of the myocardium and/or pericardium. Patients might have symptoms and signs consistent with myocarditis, pericarditis, or both. For the purpose of surveillance reporting, patients with myocarditis or pericarditis will be reported as having myo/pericarditis. These categories are intended for surveillance purposes and not for use in individual diagnosis or treatment decisions.

Case definition for acute myocarditis

A suspected case of acute myocarditis is defined by the following criteria and the absence of evidence of any other likely cause of symptoms or findings below:

- Presence of dyspnea, palpitations, or chest pain of probable cardiac origin in a patient with either one of the following:
  - Electrocardiogram (ECG) abnormalities beyond normal variants, not documented previously, including
    - ST-segment or T-wave abnormalities

- Paroxysmal or sustained atrial or ventricular arrhythmias
- Atrioventricular (AV) nodal conduction delays or intraventricular conduction defects
- Continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy

or

- Evidence of focal or diffuse depressed left-ventricular (LV) function of indeterminate age identified by an imaging study (e.g., echocardiography or radionuclide ventriculography).

A probable case of acute myocarditis, in addition to the above symptoms and in the absence of evidence of any other likely cause of symptoms, has one of the following:

- Elevated cardiac enzymes, specifically, abnormal levels of cardiac troponin I, troponin T, or creatine kinase myocardial band (a troponin test is preferred)
- Evidence of focal or diffuse depressed LV function identified by an imaging study (e.g., echocardiography or radionuclide ventriculography) that is documented to be of new onset or of increased degree of severity (in the absence of a previous study, findings of depressed LV function are considered of new onset if, on followup studies, these findings resolve, improve, or worsen)

or

- Abnormal result of cardiac radionuclide imaging (e.g., cardiac magnetic resonance imaging [MRI] with gadolinium or gallium-67 imaging) indicating myocardial inflammation

A case of acute myocarditis is confirmed if histopathologic evidence of myocardial inflammation is found at endomyocardial biopsy or autopsy.

Case definition for acute pericarditis

A suspected case of acute pericarditis is defined by the presence of

- Typical chest pain (i.e., pain made worse by lying down and relieved by sitting up and/or leaning forward) and
- No evidence of any other likely cause of such chest pain

A probable case of acute pericarditis is a suspected case of pericarditis, or a case in a person with pleuritic or other chest pain not characteristic of any other disease, that, in addition, has one or more of the following:

- Pericardial rub, an auscultatory sign with one to three components per beat
- ECG with diffuse ST-segment elevations or PR depressions without reciprocal ST depressions that are not previously documented
- Echocardiogram indicating the presence of an abnormal collection of pericardial fluid (e.g., anterior and posterior pericardial effusion or a large

posterior pericardial effusion alone)

Note: A case of acute pericarditis is confirmed if histopathologic evidence of pericardial inflammation is evident from pericardial tissue obtained at surgery or autopsy.

Dilated Cardiomyopathy

Surveillance Case Definition for Dilated Cardiomyopathy for Use in Smallpox Vaccine Adverse Event Monitoring and Response

Dilated cardiomyopathy (DCM) is defined by the World Health Organization as a disease of the heart muscle characterized by dilatation and impaired contraction of the left ventricle or both ventricles. It might be idiopathic, familial/genetic, viral, and/or immune, alcoholic/toxic, or associated with recognized cardiovascular disease in which the degree of myocardial dysfunction is not explained by the abnormal loading conditions or the extent of ischemic damage. Histology is nonspecific. Presentation is usually with heart failure, which is often progressive. Arrhythmias, thromboembolism, and sudden death are common and can occur at any stage. Despite full cardiac workup, the etiology of DCM often cannot be determined. Because other viruses are known to cause DCM, the occurrence of DCM after smallpox vaccination is plausible, although not previously described. Because histologic findings of DCM are often nonspecific, endomyocardial biopsy is not likely to confirm an etiologic role for vaccinia but might rule out other known etiologies of DCM (e.g., sarcoidosis and amyloidosis). The following case definition describes the structural and functional cardiac criteria and clinical conditions required to define a case of DCM for use in the smallpox adverse events monitoring and response activity.

Case definition for dilated cardiomyopathy after smallpox vaccination

Smallpox vaccinees are defined as having DCM if they meet all of the following criteria:

- Cardiac muscle dysfunction exists, characterized by ventricular dilatation (e.g., left ventricular end-diastolic dimension >55 mm) and impaired contraction of one or both ventricles (e.g., left ventricular ejection fraction $\leq$0.45)
- No evidence of DCM or congestive heart failure before vaccination, either by history (e.g., dyspnea on exertion and fatigue) or by cardiac evaluation, including chest radiography or echocardiography if available
- No other cardiac or noncardiac disease can account for the symptoms or abnormalities present. If another cardiac disease coexists, it is not sufficient to cause the degree of myocardial dysfunction present (e.g., ischemic or valvular heart disease or longstanding hypertension). No other etiology of DCM can be determined, such as alcohol or cocaine use, hypertension, morbid obesity, or other causes.

Case Classification

Case definitions are designed to identify the entities under surveillance, not to define the certainty of an etiologic relation between the entities under surveillance and vaccinia exposure. Thus, cases are classified as suspected if they have compatible clinical features but either further investigation is required or investigation of the case did not provide enough supporting evidence for the diagnosis. Cases are classified as probable if they have compatible clinical features and information is supportive of, but not definitive for, the diagnosis. Cases are classified as confirmed if pathognomonic findings or other evidence definitely supporting the diagnosis is documented. In certain instances, confirmation is made on the basis of verification of the presence of vaccinia or of orthopox virus DNA by culture or polymerase chain reaction (PCR) detection. Confirmation also might be determined on the basis of other evidence in instances in which vaccinia presence is not a pathognomonic feature of the entity under surveillance (e.g., myocarditis or pericarditis, both of which are believed to be an immune-mediated response to vaccination rather than mediated through vaccinia viral infection).

Classification of certain smallpox adverse vaccine reactions can be confounded by lack of information or the absence of pathognomonic findings. This is illustrated by the limited understanding of the vaccinia virus' pathogenesis and the relevance of vaccinia testing in conditions such as postvaccinial CNS diseases and fetal vaccinia. No large-scale study examining the cerebral spinal fluid (CSF) of smallpox vaccinees exists; therefore, the significance of the presence or absence of vaccinia neutralizing antibodies or vaccinia virus recovered from the CSF of a vaccinee with CNS findings is not fully understood. Testing for the presence or absence of vaccinia virus cannot confirm or refute a smallpox vaccine-associated etiology for these conditions. Conversely, the inability to recover vaccinia virus from burnt-out lesions from an infant exposed to vaccinia in utero and born with skin lesions compatible with fetal vaccinia does not mean that intrauterine infection did not occur. To address these limitations, the suspected category for these adverse reactions allows a clinically compatible case with indeterminate or no testing to remain under consideration.

Vaccinia Laboratory Diagnostics

The smallpox vaccine is made from live vaccinia virus, a species of the Orthopoxvirus genus, and protects against smallpox disease. It does not contain the related Orthopoxvirus variola, which is the causative agent of smallpox disease. When evaluating a reported adverse event after smallpox vaccination, standard laboratory testing should be conducted to rule out other infections, including viral infections (e.g., herpes zoster, varicella, enteroviruses, and herpes simplex). During an outbreak of other orthopoxviruses (e.g., monkeypox and smallpox), specific testing also should be completed for these viruses.

Laboratory testing for vaccinia is still largely a research tool assisting the evaluation, diagnosis, and treatment of adverse reactions after smallpox vaccination. Testing is available through the Laboratory Response Network (LRN), which can be accessed through state and local health departments with confirmatory testing at CDC. Diagnostic techniques that can aid in the detection of vaccinia include electron microscopy (EM), viral culture, and PCR. Although these tests can identify orthopoxviruses, only certain PCR tests or biologic characterization of viral growth on chick chorioallantoic membrane specifically identifies the presence of vaccinia virus. Positive results for EM, PCR, and viral

culture should be interpreted with caution. EM or culture results compatible with orthopox virus and presumed to be vaccinia might be another zoonotic orthopox virus or, in the worst case scenario, variola itself. Experience with vaccinia diagnostics is limited. Molecular contamination resulting in false-positive PCR results can occur. Therefore, use of appropriate controls is essential. PCR techniques, which test for orthopoxvirus nucleic acid presence, at LRN have undergone multicenter validation studies, and these data along with clinical experience with these assays is being compiled to enable the U.S. Food and Drug Administration to review the test reagents and assay for wider diagnostic use. Serologic testing of single serum samples for vaccinia is of limited value because it cannot discern existing immunity from recent infection. Testing of paired acute and convalescent sera antibody titers is rarely available during initial assessment of a suspected vaccinia adverse event.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- The smallpox vaccine surveillance case definitions presented in the report can be used in future vaccination programs to ensure uniform reporting guidelines and case classification.
- Accurate classification of vaccinia adverse reactions is necessary for appropriate use of vaccinia immune globulin (VIG) and cidofovir for the treatment of select vaccinia reactions.

POTENTIAL HARMS

Positive results for electron microscopy (EM), polymerase chain reaction (PCR), and viral culture should be interpreted with caution. EM or culture results compatible with orthopox virus and presumed to be vaccinia might be another zoonotic orthopox virus or, in the worst case scenario, variola itself. Experience with vaccinia diagnostics is limited. Molecular contamination resulting in false-positive PCR results can occur.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

Surveillance case definitions rely on a constellation of clinical, laboratory, and epidemiologic criteria for classification. They are not intended to replace clinical

judgment and should not be used to direct individual patient care, assess causality, or determine disability compensation or reimbursement for medical care. The definitions have been developed specifically for the surveillance of adverse events during the voluntary Department of Health and Human Services (DHHS) civilian smallpox preparedness and response program and might not apply to vaccinees in other settings (e.g., clinical trials). These surveillance case definitions might not apply to the international community, which administers non-New York City Board of Health (NYCBOH) vaccinia strains and faces different considerations in health-care use and surveillance systems. These case definitions are a component of a dynamic surveillance process. As knowledge and experience increase, they might be modified or improved. Ongoing input from health-care providers and health departments are important for the successful implementation and use of these case definitions.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

These case definitions and reporting guidelines were used by the Centers for Disease Control and Prevention (CDC) and the Office of the Assistant Secretary of Defense for Health Affairs during the mandatory Department of Defense (DoD) and voluntary U.S. Department of Health and Human Services (DHHS) smallpox vaccination programs that were designed to increase national preparedness in the event of a biologic terrorism attack.

Surveillance Results and Outcome

The voluntary DHHS civilian smallpox preparedness and response program established adverse event case monitoring capacity and response within CDC and state and local health departments. Data collected were derived from the standardized case definitions and enabled rapid classification, reporting, and the ability to compare adverse reaction surveillance data from various sources.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Pocket Guide/Reference Cards
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Casey C, Vellozzi C, Mootrey GT, Chapman LE, McCauley M, Roper MH, Damon I, Swerdlow DL. Surveillance guidelines for smallpox vaccine (vaccinia) adverse reactions. MMWR Recomm Rep 2006 Feb 3;55(RR-1):1-16. [43 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The Centers for Disease Control and Prevention (CDC), their planners, and their content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Pocket reference guide for the smallpox vaccine adverse events. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2002. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the CDC Web site.

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. To order copies of the pocket guide please see the Immunization Educational and Training Materials (99-7392) Brochure - Smallpox Vaccination, Method and Reactions, 2002.

Additional information regarding smallpox preparation and response activities is available from the CDC Web site.

Additionally, a Continuing Education activity is available from the Centers for Disease Control and Prevention (CDC) Web site.

Related Guideline

Cono J, Casey CG, Bell DM. Smallpox vaccination and adverse reactions. Guidance for clinicians. MMWR Recomm Rep 2003 Feb 21;52(RR-4):1-28. See the National Guideline Clearinghouse (NGC) summary.

PATIENT RESOURCES

The following are available:

- Fact sheets: smallpox basics for the general public. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan.
- Smallpox pre-vaccination information packet. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan. 34 p.
- Vaccine information statement. What you need to know. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2003 Jan. 3 p. (Available in English and Spanish).

Electronic copies of these and other related materials are available from the CDC Web site.

NGC STATUS

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